

**REMARKS**

Entry of the foregoing amendment is hereby requested. By the foregoing amendment, claim 17 has been amended to insert the phrases: “selected from a colorectal tumor, a gastric tumor and an endometrial tumor,” after “tumor” in line 1 of the claim and to specify that poly(A) tracts are those at positions 4393-4400 and 4582-4590 of SEQ ID NO:3. These changes are supported throughout the specification, for example at page 18, lines 7-19, page 10, lines 12-20, and page 33, lines 1-5.

Claim 18 has been amended to specify that the poly(A) tract is the (A)<sub>8</sub> tract of positions 4393-4400 of SEQ ID NO:3. This amendment is supported in the specification for example at page 18, lines 7-19.

Claim 19 has been amended to specify that the poly(A) tract is the (A)<sub>9</sub> tract of positions 4582-4590 of SEQ ID NO:3. This amendment is supported in the specification for example at page 18, lines 7-19.

Claim 22 has been amended to add the phrase, “a decrease of one or two adenosine nucleotides in said poly(A) tract indicates that the tumor is MSI-positive.” This amendment is supported throughout the specification, for example at page 18, lines 7-19.

These amendments are fully responsive to the sole outstanding ground of rejection, as discussed in more detail below. Applicants therefore submit that the amendment places the instant application in condition for allowance and thus should be entered.

The pending claims are 17-23.

The Claim Amendments Overcome The § 112, First Paragraph, Rejection

In the last Office Action, claims 17-23 were rejected under 35 U.S.C. § 112, First Paragraph, as allegedly lacking enablement. According to the Office Action, the specification is not enabling for a method of determining MSI status of any tumor. However, the Office Action indicated that the specification is enabling for a method of determining MSI status of a colorectal tumor, a gastric tumor and an endometrial tumor comprising determining in the tumor the number of adenosine (A) nucleotides in a poly(A) tract located at positions 4390-4400 or 4582-4590 of SEQ ID NO:3, wherein a decrease of one or two A nucleotides in said poly(A) tract indicates that the tumor is MSI-positive. (Office Action, page 3, lines 2-6). Applicants submit that the foregoing amendment is sufficient to overcome the rejection under 35 U.S.C. § 112, first paragraph.

Without conceding the propriety of the rejection, Applicants have amended claim 17 to recite the three specific tumor types that the Office Action identified as being supported by an enabling disclosure. Additionally, claim 17 has been amended to specify that the poly(A) tracts to be detected are those at positions 4393-4400 and 4582-4590 of SEQ ID NO:3. Applicants submit that this amendment is sufficient to overcome the rejection under 35 U.S.C. § 112, first paragraph, as the specification provides adequate teaching that a change in the number of A residues in the poly(A) tracts at positions 4393-4400 and 4582-4590 of SEQ ID NO:3 will result in a frameshift error in RIZ in a tumor, which is correlated with MSI status.

The question of adequacy of disclosure in the context of § 112, first paragraph, is whether the person of skill in the art could have practiced the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 735, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The key word is “undue,” not “experimentation,” as the law permits a fairly large amount of

experimentation so long as it is not “undue”. *Id.* The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Id.* The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Id.*

Applicants submit that, following the teaching of the specification and the knowledge of those skilled in the art, it would not require undue experimentation for one of skill in the art to determine whether one of the indicated poly(A) tracts had an increased or decreased number of A residues and thereby determine the MSI status of one of the named tumors. As taught in the specification, a deviation from the normal number of A residues in a poly(A) tract will result in a reading frame shift. Frameshift mutations in either tract, caused by an addition or deletion of an A residue, are predicted to lead to loss of the C-terminal domain of the RIZ protein that is involved in PR binding. (See specification, page 18, lines 16-19). There is no reasoned basis for a person skilled in the art to doubt that an increase in A residues in one of the indicated poly(A) tracts would result in a frameshift reading error. Indeed, this is precisely what one of skill in the art would expect, as reflected at page 18 of the specification. There is no justification for concluding that detecting an increase in A residues would require greater experimentation than detecting a decrease of one or two A residues.

Moreover, methods of determining the number of A residues are well known in the art. (Specification, page 18, lines 20-21). Thus, while a person skilled in the art might have to undertake some experimentation to determine that a poly(A) in a RIZ polynucleotide of a tumor had more A residues than the corresponding poly(A) of SEQ ID NO:3, such experimentation

would not be undue. Applicants have identified both the gene (SEQ ID NO:3) and the precise positions (4393-4400 and 4582-4590 of SEQ ID NO:3) at which changes in the number of A residues in the poly(A) tracts indicate MSI+ status. All that remains for the person of skill in the art to do is to determine the number of A residues in a poly(A) tract of the RIZ polynucleotide in a tumor and compare that number to the number of A residues in the corresponding poly(A) tract of the RIZ polynucleotide of SEQ ID NO:3. The amount of experimentation necessary to detect an increased number of poly(A) tracts would be expected to be very similar, if not identical, to the amount of experimentation necessary to detect a decrease of one or two A residues, which is specifically exemplified in the specification. Thus, to the extent that detection of an increased number of A residues in a poly(A) tract would require some experimentation, that experimentation would not be unduly burdensome in that it is no more than would be necessary to determine a decrease of one or two A residues.

The Office Action fails to provide an adequate basis for positing that detection of an increased number of A residues would require undue experimentation. Although the Office Action cites references that demonstrate that a decrease of one or two A residues in a poly(A) tract result in a frameshift reading error, the Office Action provides no evidence whatsoever that an increase in A residues in a poly(A) tract would not result in a frameshift reading error. Nor does the Office Action provide evidence that detection of an increase in A residues in a poly(A) tract would require any more experimentation than would detection of a decrease of one or two A residues in a poly(A) tract. Given this paucity of evidence against enablement, and given the clear teaching of the specification, which has not been rebutted, the cited references simply fail to provide the necessary basis for doubting the objective enablement of the claims as amended.

As the Office Action fails to provide adequate basis for doubting the objective enablement of amended claim 17 as discussed above, the § 112, first paragraph rejection is untenable. The amendment to claim 17 should therefore be entered and the claim allowed.

Each of claims 18-23 depend directly or ultimately from claim 17. Accordingly, Applicants submit that, upon entry of the amendment, claims 17-23 are in condition for allowance, for the same reasons as stated above for claim 17.

Additional Reasons For Allowability Of Claim 22

Upon entry of the foregoing amendment, claim 22 has been amended to further recite that a decrease of one or two adenosine nucleotides in said poly(A) tract indicates that the tumor is MSI-positive. As the Office Action specifically indicates that the disclosure is enabling for such a claim, Applicants submit that subject matter of claim 22 is allowable. Therefore, even if claims 17-21 and 23 are not allowed, the amendment to claim 22 should be entered, as it would reduce issues on appeal by removing the rejection of claim 22.

**CONCLUSION**

In light of the Amendments and Remarks herein, Applicants submit that claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he/she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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